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EXAMINER	
POPA, ILEANA	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,909	BRON, DENIS	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,9-11,13-15,17-19,21-25 and 27-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 6, 9-11, 13-15, 17-19, 21-25, and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 4, 7, 8, 12, 16, 20 and 26 have been cancelled. Claims 1, 2 and 27 have been amended.

Claims 1-3, 5, 6, 9-11, 13-15, 17-19, 21-25, and 27-29 are pending and under examination.

2. The rejection of claims 1-3, 5, 6, 9, 10, 13, 14, 17, 18, 21, and 27 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in response to Applicant's amendments to the claims filed on 11/17/2009.

All rejections pertaining to claim 27 are withdrawn in view of Applicant's amendment to the claim filed on 11/17/2009. Specifically, Applicant deleted reference to the phiC31 integrase and introduced the new limitation of transposase.

Claim Listing

3. It is noted that the instant claims amendments are not compliance with 37 CFR 1.121 or 1.4 because the changes to claim 27 are not underlined.

Response to Arguments

Priority

4. Applicant disagrees with the priority determination expressed in the Office Action. Applicant argues that EPO 02014991.0 does provide support for the use of the NCAM

Ig loop domains I, II, and III (See page 1, line 27 through page 2, line 4 of EPO 02014991.0), as well as the use of an integrase (See page 2, line 32 through page 3, line 22 of EPO 02014991.0). Specifically, for NCAM, the specification of EPO 02014991.0 states "a cell adhesion molecule or a fragment thereof wherein cell adhesion molecule is selected from the group consisting of ... NCAM (neural cell adhesion molecule) ...." (See page 1, lines 32-35). The immunoglobulin (Ig) loop domains I, II, and III in the current specification constitute a fragment of the NCAM cell adhesion molecule. Moreover, with respect to the use of integrase, the specification of EPO 02014991.0 states that the expression construct may be intended for chromosomal integration. (See page 3, lines 12-13). A preferred embodiment of the invention uses transposase, a member of the RNase superfamily of proteins, which also includes retroviral integrases. One of ordinary skill in the art would recognize that an expression construct encoding for an integrase is similar to that of a transposase in that the expression construct would be intended for chromosomal integration. Thus, support is present in the specification of the foreign priority document for the Ig loop domains of NCAM because they are a fragment of NCAM, and support is present for an expression vector containing integrase, because it is intended for chromosomal integration. Therefore, the priority date of the present application is at least July 10, 2002, the date of filing of EPO.

Applicant's arguments are acknowledged; however, they are not found persuasive for the following reasons:

With respect to the Ig loop domains I, II, and III, EPO 02014991.0 only discloses a broad genus of NCAM fragments; disclosure of such a broad genus does not provide support for specifically selecting the Ig loop domains I, II, and III as the species encompassed by the genus. Furthermore, the disclosure of one species of a broad genus does not provide support for the whole genus or for another species encompassed by the genus. Therefore, the disclosure of telomerase in EPO 02014991.0 does not provide support for specifically selecting an integrase. A transposase is not the same with an integrase.

Information Disclosure Statement

5. Applicant argues that an English translation of the reference DE 100 56 136 from the Information Disclosure Statement filed 1/10/2005 is U.S. Patent Publication No. 2004/0191303. The reference DE 100 56 136 was cited in the International Search Report for the corresponding PCT/CH03/00453, which claims priority to EPO 02014991.0, which this application also claims priority to. The International Search Report was provided to the Office at the time of National Phase filing of the present U.S. application. The cover sheet of U.S. Patent Publication No. 2004/0191303 shows at item 30 that it corresponds to DE 100 56 136. Thus, Applicant requests that the Office make record that DE 100 56 136 has been considered in the present application.

Applicant's arguments are acknowledged; however they are not found persuasive because, even if U.S. Patent Publication No. 2004/0191303 claims foreign priority to DE 100 56 136, a U.S. Patent Publication is not necessarily an exact

translation of its foreign priority document. If Applicant wishes that DE 100 56 136 document be considered, Applicant must submit an English translation of the document.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-3, 5, 6, 22 and 23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al. (PGPUB 2005/0037445), in view of each Maurer et al. (Expert Opin Biol Ther, 2001, 1: 923-947), Groth et al. (Proc. Natl. Acad. Sci. USA, 2000, 97: 5995-6000), Schreier et al. (J Biol Chem, 1994, 269: 9090-9098), and Ranheim et al. (Proc Natl Acad Sci USA, 1996, 93: 4071-4075).

Poulsen et al. teach a delivery system for cDNAs encoding therapeutic proteins the system comprising the cDNAs operably linked to a gene expression construct, a binding partner capable of associating with a cell surface receptor (i.e., a targeting moiety), and polycations, wherein the polycations form particles comprising the nucleic acid in their internal compartment and wherein the polycations form a bridge between the nucleic acid and the targeting moiety, i.e., the targeting moiety is on the particle surface; the system could further comprise a peptide providing nuclear localization signal coupled to the cDNA (claims 1, 5, 6, 22, and 23) (p. 33, paragraphs 0390-0394, p. 34, paragraphs 0412-0418, p. 37, paragraphs 0463 and 0464, p. 39, paragraphs

0563-0565, 0570, 0571, and 0577, p. 54, paragraph 0824). Poulsen et al. teach that the cDNA could be a PNA, i.e., they teach PNA-linked peptide (claim 23) (p. 6, paragraph 0099). Poulsen et al. also teach that the targeting moiety can be NCAM or NCAM IgI+II or IgIII domains (claim 1) (p. 26, paragraph 0264, p. 29, paragraph 0335, p. 30, paragraphs 0346, 0355, and 0357, p. 31, paragraphs 0358-0360).

Although Poulsen et al. teach that liposomes in general could be used to deliver nucleic acids (p. 1, paragraph 0004), they do no specifically teach liposomes as the bridge between the nucleic acid and the targeting moiety (claim 1). Maurer et al. teach liposomes as the leading delivery system for the *in vivo* administration of nucleic acids (Abstract, p. 941, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Poulsen et al. by substituting the polycations with liposomes, with a reasonable expectation of success. The motivation to do so is provided by Maurer et al., who teach liposomes as the leading delivery system for systemic administration of nucleic acids, wherein liposomes are versatile carriers because they can be easily modified by insertion of diverse molecules, such as targeting ligands, to suit any particular application (p. 923, column 1, p. 926, paragraph bridging p. 927, p. 927, column 1, last paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that liposomes can be successfully used to target nucleic acids to the cell/tissue of interest.

Although Poulsen et al. and Maurer et al. teach targeting liposomes by using an NCAM fragment comprising the IgI and IgII domains or an NCAM fragment comprising

IgIII domain as targeting ligands, they do not teach using a fragment comprising all IgI, IgII, and IgIII domains of NCAM (claim 2). However, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al. and Maurer et al. by combining their IgI, IgII, and IgIII domains into one fragment for increased binding to NCAM on the target cell surface, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because the art teaches that, beside the IgI and IgII domains, the IgIII domain also contributes to the binding to NCAM (see Poulsen et al., p. 31, paragraphs 0358-0360; Ranheim et al., p. 4074, column 2, and Fig. 6). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that all three Ig NCAM domains are involved in homophilic binding to the NCAM molecule expressed on the surface of the target cell.

Poulsen et al., Maurer et al., and Ranheim et al. do not teach a nucleic acid encoding the phiC31 integrase (claim 1). However the prior art teaches site-specific integration into mammalian cell genome for research and gene therapy, wherein site-specific integration is used to avoid undesirable mutations in important genes and wherein specific and efficient site-specific integration is achieved by using the phiC31 integrase (see Groth et al., Abstract, p. 5995, column 2, p. 5998, p. 5999, columns 1 and 2, p. 6000, columns 1 and 2). Based on these teachings, one of skill in the art would have known to use phiC31 integrase when the stable and specific integration of genes of interest into the genome of a target cell was required. Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the

delivery system of Poulsen et al. and Maurer et al. by further including the phiC31 integrase, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain stable and targeted integration of transgenes into a target cell for research or gene therapy purposes. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the prior art teaches phiC31 integrase can be successfully used to direct site-specific integration of transgenes into the genome of mammalian cells (see Groth et al., p. 6000, column 1).

Poulsen et al., Maurer et al., Groth et al. and Ranheim et al. do not teach linking the NCAM via a hydrophobic anchor molecule (claim 3). However, such is suggested by the prior art. For example, Schreier et al. teach targeting liposomes to specific cells by inserting ligands into liposomes via a glycosylphoshaphatidylinositol (GPI) anchor (i.e., a hydrophobic anchor molecule) (Abstract, p. 9092, columns 1 and 2, p. 9093, columns 1 and 2, p. 9097, column 1, paragraph bridging column 2, 9098, column 1, last paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al., Maurer et al. and Ranheim et al. by inserting the NCAM ligand via a GPI anchor, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Schreier et al. teach their method as simple and convenient (p. 9090, column 2, first full paragraph). One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful use of GPI anchors to incorporate proteins into liposomes.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

8. Claims 1-3, 5, 6, 9, 10, 13, 14, 17, 18 and 21-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al. taken with each Maurer et al., Groth et al., Schreier et al., and Ranheim et al., in further view of both Sato et al. (J. Drug Target., 2001, 9: 201-207, of record) and Gosselin et al. (Bioconjugate Chem., 2001, 12: 989-994, of record).

The teachings of Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. are applied as above for claims 1-3, 5, 6, 22, and 23. Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. do not teach their delivery system as further comprising a DNA compacting agent (claims 9 and 10), nor do they teach a chemical inclusion for breaching the endosomal barrier (claim 21). Sato et al. teach that introducing cationic polymers such as high molecular weight PEI into DNA/liposome complexes enhances their transfection efficiency by condensing the DNA and promoting the escape of the DNA from the endosomal compartment (i.e., PEI breaches the endosomal barrier) (p. 202, column 1, last paragraph, and column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the system of Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. according to the teachings of Sato et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do because the art

teaches that addition of PEI enhance the transfection efficiency of complexes made only of DNA and liposomes.

Poulsen et al., Maurer et al., Groth et al., Schreier et al., Ranheim et al., and Sato et al. do not teach their PEI as being reversibly cross-linked via a thio bridge (claims 13, 14, 17, and 18). Gosselin et al. teach replacing the cytotoxic high molecular PEI with conjugates consisting of low molecular weight PEI cross-linked via thio bridges, wherein such conjugates are less cytotoxic because the thio bridges are cleaved in the reducing environment of the cytoplasm resulting in less cytotoxic intracellular low molecular weight PEI which has an easier access to the transcription machinery (Abstract, p. 989, column 2, p. 990, Fig. 1 and 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al., Maurer et al., Groth et al., Schreier et al., Ranheim et al., and Sato et al. by replacing their high molecular weight PEI with the cross-linked low molecular weight PEI of Gosselin et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain a less cytotoxic DNA delivery system. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that cross-linked low molecular weight PEI can be successfully used to deliver DNA to cells.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

9. Claims 1-3, 5, 6 and 22-25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al. taken with each Maurer et al., Groth et al., Schreier et al., and Ranheim et al., in further view of Li et al. (Acta Anaesthesiol. Sin., 2000, 38: 207-215, Abstract).

The teachings of Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. are applied as above for claims 1-3, 5, 6, 22 and 23. Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. do not teach Bcl-2 delivery (claims 24 and 25). However, doing such is suggested by the prior art which teaches that liposomes can be successfully used to deliver nucleic acids encoding Bcl-2 (see Li et al., Abstract). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the system of Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. by replacing their DNA with a DNA encoding Bcl-2 to achieve the predictable result of delivery Bcl-2 to a subject in need of treatment with anti-apoptotic agents. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

10. Claim 29 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al., in view of each Maurer et al., Smith et al. (U.S. Patent No. 6,329,501), and Charlton et al. (Developmental Biology, 2000, 221: 112-119).

Poulsen et al. teach a delivery system for cDNAs encoding therapeutic proteins (i.e., pharmaceutical agents) the system comprising the cDNAs operably linked to a gene expression construct, a binding partner capable of associating with a cell surface

receptor (i.e., a targeting moiety), and polycations, wherein the polycations form particles comprising the nucleic acid in their internal compartment and wherein the polycations form a bridge between the nucleic acid and the targeting moiety, i.e., the targeting moiety is on the particle surface (p. 33, paragraphs 0390-0394, p. 34, paragraphs 0412-0418, p. 39, paragraphs 0563-0565, 0570, 0571, and 0577). Poulsen et al. teach that the targeting moiety can be NCAM or NCAM IgI+II or IgIII domains (p. 26, paragraph 0264, p. 29, paragraph 0335, p. 30, paragraphs 0346, 0355, and 0357, p. 31, paragraphs 0358-0360).

Although Poulsen et al. teach that liposomes in general could be used to deliver nucleic acids (p. 1, paragraph 0004), they do no specifically teach liposomes as the bridge between the nucleic acid and the targeting moiety (claim 1). Maurer et al. teach liposomes as the leading delivery system for the *in vivo* administration of nucleic acids (Abstract, p. 941, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Poulsen et al. by substituting the polycations with liposomes, with a reasonable expectation of success. The motivation to do so is provided by Maurer et al., who teach liposomes as the leading delivery system for systemic administration of nucleic acids, wherein liposomes are versatile carriers because they can be easily modified by insertion of diverse molecules, such as targeting ligands, to suit any particular application (p. 923, column 1, p. 926, paragraph bridging p. 927, p. 927, column 1, last paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the

art teaches that liposomes can be successfully used to target nucleic acids to the cell/tissue of interest.

Although Poulsen et al. and Maurer et al. teach delivery of therapeutic transgenes, they do not specifically teach a transgene encoding the human dystrophin. Smith et al. teach using liposomes coated with targeted ligands to specifically deliver the dystrophin gene to the muscle cells of patients suffering from Duchenne muscular dystrophy (Abstract, column 2, lines 50-60, column 5, lines 62-67, column 5, lines 3-10). Although Smith et al. do not specifically teach targeting by using NCAM or a fragment thereof, the prior art teaches that muscle cells express NCAM on their surface (see Charlton et al., Abstract, p. 112, column 2). Based on these teachings in the art as a whole, one of skill in the art would have known that the delivery system of Poulsen et al. and Maurer et al. (i.e., liposomes coated with NCAM or fragments thereof) could be used to deliver transgenes to muscle cells. Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to use the system of Poulsen et al. and Maurer et al. to deliver the dystrophin gene of Smith et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to treat patients affected by Duchenne muscular dystrophy, as taught by Smith et al. One of skill in the art would have been expected to have a reasonable expectation of success in using NCAM-coated liposomes to target transgenes to the muscle cells expressing NCAM on their surface because the art teaches that NCAM is involved in homophilic binding to other NCAM molecules (see Poulsen et al., p. 31, paragraphs 0358-0360).

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

11. Claims 11, 15, 19, and 29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al. taken with each Maurer et al., Smith et al., and Charlton et al., in further view of both Sato et al. and Gosselin et al.

The teachings of Poulsen et al., Maurer et al., Smith et al., and Charlton et al. are applied as above for claim 29. Poulsen et al., Maurer et al., Smith et al., and Charlton et al. do not teach their delivery system as further comprising a DNA compacting agent (claim 11). Sato et al. teach that introducing cationic polymers such as high molecular weight PEI into DNA/liposome complexes enhances their transfection efficiency by condensing the DNA and promoting the escape of the DNA from the endosomal compartment (i.e., PEI breaches the endosomal barrier) (p. 202, column 1, last paragraph, and column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the system of Poulsen et al., Maurer et al., Smith et al., and Charlton et al. according to the teachings of Sato et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do because the art teaches that addition of PEI enhance the transfection efficiency of complexes made only of DNA and liposomes.

Poulsen et al., Maurer et al., Smith et al., Charlton et al., and Sato et al. do not teach their PEI as being reversibly cross-linked via a thio bridge (claims 13, 14, 17, and 18). Gosselin et al. teach replacing the cytotoxic high molecular PEI with conjugates

consisting of low molecular weight PEI cross-linked via thio bridges, wherein such conjugates are less cytotoxic because the thio bridges are cleaved in the reducing environment of the cytoplasm resulting in less cytotoxic intracellular low molecular weight PEI which has an easier access to the transcription machinery (Abstract, p. 989, column 2, p. 990, Fig. 1 and 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al., Maurer et al., Smith et al., Charlton et al., and Sato et al. by replacing their high molecular weight PEI with the cross-linked low molecular weight PEI of Gosselin et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain a less cytotoxic DNA delivery system. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that cross-linked low molecular weight PEI can be successfully used to deliver DNA to cells.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the rejections above on the grounds that Poulsen discloses targeting complexes that are capable of being internalized into cells. The targeting complexes in Poulsen are polycations. The polycations taught in Poulsen provide a binding agent to associate with a cell surface molecule. (See paragraphs [0079] and [0087] of Poulsen). As recognized in the Office Action, Poulsen does not specifically teach liposomes comprising DNA as a bridge between a nucleic acid and a targeting

moiety. Thus, Poulsen does not teach liposomes comprising DNA in their internal compartment and having the cell adhesion molecule NCAM or a fragment thereof. Further, Poulsen is silent regarding targeting complexes that comprise "a molecule encoding a chromosomal integration activity" as claimed in claim 1.

The Office Action's proposed modification of Poulsen, i.e., substitute a liposome for the polycation in Poulsen, results in DNA somehow covalently linked to the liposome. The proposed modification of Poulsen does not result in DNA placed within an internal compartment of the liposome, as claimed in claim 1. Thus, even if the proposed combination of Poulsen and Maurer is deemed proper, it does not result in DNA placed within an internal compartment of the liposome, as claimed in claim 1. Further, one of ordinary skill in the art at the time the invention was made would not have been motivated to modify Poulsen to provide liposomes which comprise in their internal compartment a pharmaceutical agent and which have linked to their external surface the cell adhesion molecule NCAM or a fragment thereof, wherein said pharmaceutical agent is DNA and said delivery system comprises a molecule encoding a chromosomal integration activity, as claimed in amended claim 1. As taught by Poulsen, polycations are different from liposomes in that "polycations have the ability to compact and neutralize the charge of the delivered DNA." (See paragraph [0004] of Poulsen). Poulsen uses polycationic agents to bind DNA resulting in a complex where the negative charge of the nucleic acid molecule is completely neutralized for internalization via normal receptor-mediated endocytosis. (See paragraph [0571] of Poulsen). Moreover, in Poulsen, the binding partner (i.e., NCAM) associates with a

bioreactive species (i.e., DNA) via a nucleic acid binding agent (i.e., polycation) covalently linked to the binding partner. In Poulsen, the polycationic agent requires a source of negative charge on the nucleic acid for binding. (See paragraph [0573] of Poulsen). There is no teaching or suggestion in Poulsen to substitute a liposome for a polycation.

Indeed, Poulsen teaches away from using liposomes. Poulsen teaches that while non-viral vectors, such as liposomes and polycations, are less immunogenic, easier to produce, and do not need the safety considerations of viral vectors, liposomes and polycations have much lower transfection efficiency than viral vectors and also lack the cell specificity provided by viral vectors. (See paragraph [0004] of Poulsen). Poulsen teaches that a polycation has the unique ability to compact and neutralize the charge of delivered DNA. Poulsen teaches that modifying a polycation by placing it in a multi-component non-viral vector increases the transfection efficiency and cell specificity for therapeutic gene delivery. Poulsen does not teach how to avoid the problems of non-viral vectors by modifying liposomes. Nor does Poulsen teach how to attach NCAM or a fragment thereof via a transmembrane domain or a hydrophobic anchor molecule. Thus, one of ordinary skill in the art at the time of the present invention would not have been motivated to or have had a reasonable expectation of success to substitute the polycations required in Poulsen with liposomes.

None of the other cited references, i.e., Maurer, Groth, Schreier, Ranheim, Smith, Charlton, Sato, Gosselin, nor Li retract from Poulsen teaching that polycations must be used instead of liposomes. Also, Poulsen is silent as to the delivery system

comprising an additional molecule encoding a chromosomal integration activity. None of the other references remedy the deficiencies of Poulsen with respect to liposomes comprising chromosomal integration activity. Maurer is directed to a review of liposomes for drug delivery and discusses only conventional drugs, DNA and pDNA (See Abstract and page 936, column 1 through page 941, column 1 of Maurer). Maurer is thus completely silent regarding using molecules to integrate DNA into a host genome. Groth is directed to integrase from phi31 to carry out site-specific integration in human cells, but is totally unrelated to NCAM and does not refer to liposomes. Schreier is directed to glycosylphosphatidylinositol-anchored proteins for use as targeting molecules for liposomes, and is entirely silent regarding chromosomal integration activity (See Abstract of Schreier). Ranheim is directed to the interaction of neural cell adhesion molecules (NCAM) on two different cells and is totally unrelated to chromosomal integration activity (See Abstract of Ranheim). Sato and Gosselin do not remedy the deficiencies in the other cited references as they do not disclose a chromosomal integration activity. Li also does not remedy the deficiencies because the Abstract, as recognized in the Office Action, generally refers to a liposomal method for delivering genes into the myocardium and is silent on having a chromosomal integration activity.

Consequently, it would not have been obvious for one of skill in the art to develop the invention of claim 1 merely from the disclosures of the references cited in the Office Action. Claim 1 is therefore patentable over Poulsen in view of any combination of Maurer, Groth, Schreier, Ranheim, Smith, Charlton, Sato, Gosselin, or Li. The pending

dependent claims depend from claim 1 and are patentable for at least the same reasons as claim 1 is patentable and for the additional features recited therein.

Claim 29 is also patentable over the prior art. The Office Action concedes that Poulsen does not specifically teach liposomes as the bridge between the nucleic acid and the targeting moiety. The Office Action is incorrect to assume that, in light of Maurer, it would have been obvious to one of skill the art, at the time the invention was made, to modify the method of Poulsen et al. by substituting polycations with liposomes, with a reasonable expectation of success. As explained above, Poulsen actually teaches away from using liposomes as a leading delivery system of nucleic acids. While non-viral vectors are less efficient and specific than viral vectors, Poulsen only teaches that polycations, not liposomes, can be modified in a multi-component complex to overcome that limitation. Thus, one of ordinary skill in the art would not be motivated to combine the teaching of Maurer with Poulsen.

The Office Action also acknowledges that neither Poulsen nor Maurer teach a transgene encoding the human dystrophin. While Smith et al. teaches the targeting of the dystrophin gene to muscles, it merely teaches that peptides, which target a gene for expression in muscles, can be used to target liposomes. As noted in the Office Action, Smith is silent on using NCAM or a fragment thereof linked to the external surface of the liposome or using lipsomes with a pharmaceutical agent contained in the internal compartment. While Charlton et al. teaches that muscle cells express NCAM on their surface, one of skill the art would not have modified Poulsen with the stated references to link NCAM to the external surface of a liposome to deliver the dystrophin gene to

cells in view of Poulsen's teaching away from the use of liposomes in favor of polycations.

Sato et al. and Gosselin et al. do not remedy the deficiencies of the above mentioned references as they do not teach linking NCAM to the external surface of a liposome.

Applicant's arguments are acknowledged; however, they are not found persuasive for the following reasons:

It is noted that most of Applicant's arguments are not new and were previously addressed. The new arguments are addressed below.

Applicant argues that Poulsen teaches away from using liposomes as a delivery system of nucleic acids. This is not found persuasive. Poulsen teaches that liposomes and cationic polymers are both suitable for nucleic acid delivery (paragraph 0004); just because Poulsen further chooses to use cationic polymers and not liposomes does not take away from this teaching. MPEP clearly states that a teaching away from the invention is a teaching which renders prior art unsatisfactory for the intended purpose (MPEP 2145 [R-6] X D). There is no teaching in Poulsen that liposomes are unsatisfactory for delivering nucleic acids. The use of liposomes was routine in the prior art. The prior art teaches liposomes as a leading delivery system for nucleic acids, wherein liposomes can be modified in a multi-component complex to achieve efficient nucleic acid delivery (see the teachings of Maurer et al. above). Clearly, by reading

Poulsen and in view of the prior art, one of skill in the art would not have concluded that Poulsen taught away from using liposomes.

Applicant argues that the proposed modification would result in the DNA "somehow" covalently linked to liposomes and not encapsulated within the internal compartment. Not only is this just an assumption not supported by any evidence, but it is not clear how Applicant arrived at this conclusion. The rejection is based on replacing Poulsen's cationic polymers (which non-covalently associate with and compact nucleic acids) with liposomes, which encapsulate the nucleic acid. That liposomes function by encapsulated the therapeutic agents within their internal compartment without formation of covalent bonds is common knowledge in the art. No covalent bond is taught by the combined teachings above. By combining the teachings of the cited art cited, one of skill in the art would have obtained liposomes comprising nucleic acids within their internal compartment and targeting NCAM fragments exposed on their outer surface.

For the reasons set forth above, Applicant's arguments are not found persuasive and the rejections are maintained.

12. Claims 1, 2, 5, 6 and 28 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy (U.S. Patent No. 6,635,476), in view of each Poulsen et al., Ranheim et al. and Groth et al.

Murphy teaches a system for the delivery of genes encoding therapeutic polypeptides (i.e., cDNA operably linked to a gene expression construct), the system comprising liposomes having the gene in their internal space and targeting ligands on

their external surface for binding to specific cell surface receptors, wherein the receptors can be NCAM (claims 1, 5, 6, and 28) (Abstract, column 3, lines 5, 6, and 59-63, column 5, lines 24-27, column 9, lines 45-63, column 13, lines 25-46).

Although Murphy teaches NCAM as the cell surface receptor, he does not specifically teach that the targeting ligand is NCAM or an NCAM fragment comprising the first three Ig domains as targeting ligands (claims 1 and 2). Poulsen et al. teach NCAM and NCAM fragments comprising the IgI and IgII domains or the IgIII domain as targeting ligands capable of homophilic binding to another NCAM molecule on the surface of a target cell (p. 3, paragraph 0036, p. 4, paragraphs 0048-0051, p. 28, paragraphs 0288 and 0290, p. 29, paragraphs 0355, p. 31, paragraphs 0358-0360). It would have been obvious to one of skill in the art, at the time the invention was made, to modify Murphy's delivery system by using one of the targeting ligands taught by Poulsen et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Murphy teaches delivery to cells expressing NCAM on their surface and because Poulsen et al. teach their fragments as capable of specific delivery to NCAM-expressing cells. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because Murphy teaches that any ligand that binds NCAM can be used with their system (column 13, lines 50-61). With respect to the limitation recited in claim 2, it would have been obvious to one of skill in the art, at the time the invention was made, to combine the IgIII and IgI+IgII fragments of Poulsen et al. to obtain an IgI+IgII+IgIII fragment, for increased binding to NCAM on the target cell surface, with a reasonable expectation of success.

One of skill in the art would have been motivated to do so because the art teaches that, besides the beside IgI and IgII domains, the IgIII domain, also contributes to the binding to NCAM (see Poulsen et al., p. 31, paragraphs 0358-0360; Ranheim et al., p. 4074, column 2, and Fig. 6). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that all three Ig NCAM domains are involved in homophilic binding to the NCAM molecule expressed on the surface of the target cell.

Murphy, Poulsen et al., Ranheim et al. do not teach a nucleic acid encoding the phiC31 integrase (claims 1 and 27). However the prior art teaches site-specific integration into mammalian cell genome for research and gene therapy, wherein site-specific integration is used to avoid undesirable mutations in important genes and wherein specific and efficient site-specific integration is achieved by using the phiC31 integrase (see Groth et al., Abstract, p. 5995, column 2, p. 5998, p. 5999, columns 1 and 2, p. 6000, columns 1 and 2). Based on these teachings, one of skill in the art would have known to use phiC31 integrase when the stable and specific integration of genes of interest into the genome of a target cell was required. Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al. and Maurer et al. by further including the phiC31 integrase, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain stable and targeted integration of transgenes into a target cell for research or gene therapy purposes. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because

the prior art teaches phiC31 integrase can be successfully used to direct site-specific integration of transgenes into the genome of mammalian cells (see Groth et al., p. 6000, column 1).

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that Murphy is directed to targeted vectors "that are complexed to a targeting moiety by coordinate covalent linkages mediated by a transition metal ion" (Abstract of Murphy). Murphy makes no mention of chromosomal integration activity and using fragments of NCAM. There is no teaching or suggestion in the prior art to modify Murphy and delete the required transition metal ion of Murphy. As noted above, Poulsen teaches away from using liposomes because of their limitations of low cell specificity and efficacy, and instead teaches use of polycations to covalently bond with DNA. One of ordinary skill in the art at the time of the present invention would not have looked to the polycation system of Poulsen to try to modify and improve the system of Murphy.

Poulsen and Ranheim are discussed above as lacking disclosure related to liposomes comprising a chromosomal integration activity. Groth is directed to integrase from phi31 to carry out site-specific integration in human cells, but is totally unrelated to NCAM and liposomes. One of ordinary skill in the art would not have had a reasonable expectation of success at the time the present invention was made to combine integrase activity as taught by Groth with the teachings from Murphy and the other references. Moreover, none of the references teach linking a liposome via a

transmembrane domain or a hydrophobic anchor molecule to NCAM, as the linkages taught in the references are covalent attachments.

Accordingly, claim 1 is patentable over Murphy in view of Poulsen and Ranheim. The dependent claims depend from claim 1 and are patentable for at least the same reasons as claim 1 and for the additional features recited therein.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). None of the cited references has to teach each and every claim limitation. If they did, this would have been anticipation and not an obviousness-type rejection.

Applicant argues that there is no teaching or suggestion in the prior art to modify Murphy by replacing the coordinate covalent linkage with a transmembrane domain or a hydrophobic anchor to attach the targeting moiety to the liposomes. This argument is not material to the instant rejection which does not require modifying Murphy by replacing the coordinate covalent linkage. The rejected claims do not require a specific attachment. The rejected claims only require the presence of targeting moieties on the liposomal surface, which is taught by Murphy.

The argument that Poulsen teaches away from using liposomes has been addressed above.

Applicant's argument that one of skill in the art would not have had a reasonable expectation of success to modify Murphy by adding an integrase is not found persuasive because it is not supported by any evidence.

For the reasons set forth above, Applicant's arguments are not found persuasive and the rejection is maintained.

New Rejections

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1, 5, 6, 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy in view of each Poulsen et al., Ranheim et al. and Hackett et al. (U.S. Patent No. 6,489,458).

Murphy teaches a system for the delivery of genes encoding therapeutic polypeptides (i.e., cDNA operably linked to a gene expression construct), the system comprising liposomes having the gene in their internal space and targeting ligands on their external surface for binding to specific cell surface receptors, wherein the receptors can be NCAM (claims 1, 5, 6, and 28) (Abstract, column 3, lines 5, 6, and 59-63, column 5, lines 24-27, column 9, lines 45-63, column 13, lines 25-46).

Although Murphy teaches NCAM as the cell surface receptor, he does not specifically teach that the targeting ligand is NCAM or an NCAM fragment comprising the first three Ig domains as targeting ligands (claims 1 and 2). Poulsen et al. teach NCAM and NCAM fragments comprising the IgI and IgII domains or the IgIII domain as targeting ligands capable of homophilic binding to another NCAM molecule on the surface of a target cell (p. 3, paragraph 0036, p. 4, paragraphs 0048-0051, p. 28, paragraphs 0288 and 0290, p. 29, paragraphs 0355, p. 31, paragraphs 0358-0360). It would have been obvious to one of skill in the art, at the time the invention was made, to modify Murphy's delivery system by using one of the targeting ligands taught by Poulsen et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Murphy teaches delivery to cells expressing NCAM on their surface and because Poulsen et al. teach their fragments as capable of specific delivery to NCAM-expressing cells. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because Murphy teaches that any ligand that binds NCAM can be used with their system (column 13, lines 50-61). With respect to the limitation recited in claim 2, it would have been obvious to one of skill in the art, at the time the invention was made, to combine the IgIII and IgI+IgII fragments of Poulsen et al. to obtain an IgI+IgII+IgIII fragment, for increased binding to NCAM on the target cell surface, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because the art teaches that, besides the beside IgI and IgII domains, the IgIII domain, also contributes to the binding to NCAM (see Poulsen et al., p. 31, paragraphs 0358-0360; Ranheim et al., p. 4074,

column 2, and Fig. 6). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that all three Ig NCAM domains are involved in homophilic binding to the NCAM molecule expressed on the surface of the target cell.

Murphy, Poulsen et al., Ranheim et al. do not teach a nucleic acid encoding a transposase (claims 1 and 27). However, at the time the invention was made, delivery systems comprising nucleic acids of interest and nucleic acids encoding transposases were routinely used to introduce the nucleic acids of interest into mammalian cell genome (see Hackett et al., Abstract, column 3, lines 45-50, column 4, lines 12-26, column 14, lines 46-54, column 18, lines 52-65). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al. and Maurer et al. by further including a transposase, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain stable integration of nucleic acids of interest into a target cell for research or gene therapy purposes. One of skill in the art would have reasonably expected to be successful in doing so because the prior art teaches that transposases can be successfully used to direct stable integration of transgenes into the genome of cells.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Conclusion

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633